REMARKS/ARGUMENTS

Status of the claims

With entry of the instant amendment, claims 1-14 have been amended and new claims 15-26 have been added.

The amendments add no new matter and are fully supported throughout the application as filed. Support for new claims 15-26 can be found, *e.g.*, at page 9, line 28 bridging to page 10, line 7; page 14, lines 5-9; and page 29, lines 30-33.

Correction of status of application

The specification was objected to because the first paragraph indicates that the application is a continuation application. The Examiner indicates that the application is more accurately referred to as a divisional. The amendment to the first paragraph corrects the filing status. Also submitted herewith is a supplemental Application Data Sheet (ADS) with the correction.

Claim objections

The objection to claims 5 and 12 over the typographical error "Sso7D" is obviated by the amendments to the claims.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 2, 3, 9, and 10 are rejected as allegedly indefinite over lack of proper antecedent basis. The claims have been now amended to provide proper antecedence. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph--written description

Claims 1-14 are rejected as allegedly lacking proper written descriptive support in the specification. The Examiner contends that insufficient species are disclosed in the office action to support the genus. Specifically, the Examiner characterizes the specification as

disclosing only three species, Sso7d-ΔTaq, Sso7d-Taq, and Pfu-Sso7d, that are encompassed by the claimed genus. The Examiner further alleges that there is no disclosure of any particular structure/function relationship among the disclosed species regarding the nucleic acid binding domain and polymerases that exhibit enhanced processivity when modified with the nucleic acid binding domain. In view of these alleged shortcomings, the Examiner contends that Applicants have not described the invention sufficiently to demonstrate possession. Applicants respectfully traverse this rejection.

The standard for written description is that one of skill must demonstrate possession of the claimed invention. For a genus, this can be achieved by description of representative species or providing general structural characteristics in combination with function. The specification provides such description. First, applicants have disclosed any number of polymerases that can be modified using a nucleic acid binding domain as claimed. For example, the section beginning on page 9, line 25 details various polymerase families and polymerases within those family that can be used in accordance with the invention. Such polymerases have been widely characterized in the prior art both structurally and functionally. Furthermore, the specification provides exemplary embodiments showing the wide-ranging ability of Sso7d to enhance processivity. For example, Taq is a family A polymerase. The polymerase ΔTaq is a modified Taq polymerase that lacks the N-terminal 289 amino acids. Sso7d enhances processivity of both polymerases. Moreover, the general effects of Sso7d on polymerase processivity were evaluated using a family B polymerase, Pfu polymerase, as a further example. Although this polymerase shares little sequence identity with Taq (*see, e.g.*, the polymerase sequences provided in the specification), Sso7d also enhanced processivity of this polymerase.

The specification not only fully describes polymerases for use in the invention, but also provides description of Sso7d nucleic acid binding domains as recited in the claims. The claims recite a structural feature of the genus of Sso7d proteins for use in the invention, *i.e.*, reference SEQ ID NO:2, and provides structural and functional characteristics of proteins encompassed by the genus. For example, the specification describes Sso7d and Sac7d, which are proteins of a MW of about 7,000. The proteins are lysine-rich and have high thermal, acid and

chemical stability. The specification further describes references that disclose other Sso7d homologs and describe structural analyses of Sso7d and Sac7d when bound to DNA (*see, e.g.,* page 12, lines 8-15). The application also teaches that this DNA binding function can be used as a basis for selecting DNA binding domains that can be used to enhance polymerase processivity (see, *e.g.,* page 12, lines 5-7 and 25-29). In view of the foregoing, the application fully describes the claimed invention. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph--enablement

Claims 1-14 are rejected as allegedly lacking enablement. The Examiner contends that the specification does not provide teachings of specific regions of a DNA binding domain that can be altered relative to the reference sequence without effecting the sequence non-specific nucleic-acid-binding activity; does not teach the general tolerance of the domain to modification; does not provide a rational and predictable scheme for modifying amino acid residues of the binding domain with an expectation of obtaining the desired biological function; and does not provide sufficient guidance as to which of the possible choices for modification are likely to be successful. Applicants respectfully disagree. The specification provides multiple examples of enhancement of processivity of polymerases using Sso7d and its homologs. In addition to the general guidance regarding polymerases and Sso7d proteins provided by the specification, the examples provide data for four exemplary embodiments using two Sso7 proteins (Sso7d and Sac7d) and three polymerases (Taq, ΔTaq, and Pfu). These data provide further evidence that the claims are enabled.

Applicants have also provided a Declaration under 37 C.F.R. § 1.132 by Peter Vander Horn ("the Vander Horn Declaration") in the parent application. Applicants respectfully request that the Declaration, a copy of which is enclosed, be made of record in the instant application, as the same issues are being raised. The Vander Horn Declaration provides objective reasons further justifying the claimed genus of methods.

State of the art at the time of the invention

The Sso7d nucleic acid binding domains set forth in the claims are not derived from a novel gene. A natural variation of about 76% occurs within the family (as noted in the Vander Horn Declaration, which is discussed in greater detail below). Analyses of the structures of Sso7d and Sac7d bound to DNA have been performed by several investigators. The specification directs a practitioner to exemplary references describing such studies (*e.g.*, Baumann *et al. Structural Biol* 1:808-819, 1994 and Gao *et al., Nature Struc. Biol* 5:782-786, 1998; both cited in paragraph 44; copies provided as Exhibits 9 and 3, respectively, of the Vander Horn Declaration). Baumann *et al.* teach NMR structural analysis of the DNA binding surface of Sso7d. Gao et al. teach Sso7d-DNA structures determined using x-ray crystallography.

Similar x-ray crystallographic analysis has also been performed for the related protein Sac7d (*e.g.*, Robinson, *et al., Nature* 392:202-205, 1998, which reference is cited by Gao *et al.*). Gao *et al.* additionally compare the Sso7d-DNA complex to the Sac7d-DNA complex. Thus, at the time of the invention, those of skill in the art had extensive information available to them regarding regions and specific residues of Sso7d that are involved in the binding interaction of the protein with DNA. Accordingly, the disclosure in the application, when filed, contains sufficient information to enable one of skill in the art to make and use a DNA binding domain that would reasonably be expected to have binding activity and therefore have the ability to enhance polymerase processivity. Thus, the specification therefore properly enables the claimed methods.

Applicants have provided objective reasons justifying the percent identity set forth in the claims

Not only does the subject specification provide a full disclosure of the family of Sso7 proteins, Applicants have provided the Vander Horn declaration, which provides objective reasons justifying the 75% level of identity recited in the claims. Dr. Vander Horn explains that by following the differences between the family members, those of skill would immediately recognize where the critical and noncritical regions of the proteins are located. The family

members are a virtual roadmap to novel variants. As Dr. Vander Horn notes in his Declaration, to limit the claims to a percentage above that found within the naturally occurring variants is to ignore that nature has provided this road map for introducing mutations. Indeed, in section 13 of his declaration, Dr. Vander Horn has created a hybrid protein combining known natural variations to obtain a protein with 76% identity to Sso7d.

In addition to the natural variations between family members, any competent protein chemist readily understands that non-naturally occurring but conserved substitutions are possible throughout the primary sequences of the prototype proteins. Dr. Vander Horn explains this conventional wisdom at section 9 of his Declaration.

Furthermore, Dr. Vander Horn explains at section 10 of his Declaration that the structural features of the Archaeal protein interaction with DNA had been previously studied by workers such as Gao *et al.* Dr Vander Horn details how this information permits a practitioner to identify the critical binding domains in the proteins, which allows one of skill to focus mutations away from these critical regions so that amino acid residues may be substituted without compromising activity.

The Vander Horn Declaration thus further illustrates how one of skill in the art can use the large body of knowledge in the art to identify functional Sso7d variants having the percent identity set forth in the claims without undue experimentation.

In view of the foregoing, the application provides proper guidance such that one of skill can identify a nucleic acid binding domain as claimed and that use it to modify polymerase processivity with a reasonable expectation of success.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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of Rule 132 Declaration with Exhibits 1-10